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Review

A Review of the Adverse Effects of Peripheral Alpha-1 Antagonists in Hypertension Therapy

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Abstract

Background: Doxazosin and its role as an antihypertensive agent have come under recent scrutiny as a result of the early termination of that treatment arm in ALLHAT. It is unclear why the cardiovascular (CV) event rate in this randomized, controlled trial (RCT), especially heart failure, is higher in those treated with a doxazosin-based regimen than with a chlorthalidone based-regimen. There has been little work in the past to summarize information on peripheral alpha-1 antagonists that may be helpful in evaluating the results of this randomized controlled trial.

Methods: Using Medline and the Cochrane databases, we performed a comprehensive review of the literature on the use of peripheral alpha-1 antagonists as antihypertensive agents, focusing on available information that could explain the excess cardiovascular events observed in the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT).

Results: Minimal data were available concerning the effects of peripheral alpha-1 antagonists on CV endpoints. A multitude of short-term studies-ranging from small observational studies to short-term moderate-sized RCTs – focused on safety, efficacy, and tolerability, and some studies investigated the physiologic effects of these agents. These previously reported studies reveal associations with weight gain, fluid retention, and neurohormonal changes among various populations of those treated with peripheral alpha-1 antagonists.

Conclusion: These findings suggest several possible mechanisms by which doxazosin may be inferior to low-dose diuretics as antihypertensive therapy for the prevention of heart failure.

Background

With the publication of the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT), the role of peripheral alpha-1 antagonists in the treatment of hypertension has become controversial. The doxazosin arm of ALLHAT was stopped early, due to a doubling of the incidence of congestive heart failure in this group, as compared to the low-dose chlorthalidone arm [1]. Prior to this publication, there had been no obvious suggestion of a mechanism by which peripheral alpha-1 antagonists in general or doxazosin in particular would be inferior to chlorthalidone or would specifically cause CHF. Because ALLHAT is an active-control trial, no inferences can be made on whether this increased inci-

dence of CHF results from a harmful effect of doxazosin, a beneficial effect of chlorthalidone, or both. Nonetheless, there has been a large body of literature dedicated to the positive effects of peripheral alpha-1 antagonists on surrogate endpoints such as cholesterol levels and tolerability. In light of the results of ALLHAT, we performed a review of the literature on doxazosin, terazosin, and prazosin.

Methods

Medline and the Cochrane databases were used to identify English-language papers on peripheral alpha-1 antagonists in studies targeting cardiovascular endpoints, background physiologic literature, or any studies suggesting mechanisms leading to an inferior performance in cardiovascular endpoints. Medline was searched from 1966 to the present with the key words "doxazosin," "prazosin," "terazosin," "adrenergic alpha-antagonists," or "alpha blocker." The search was then limited to clinical trials that had "hypertension" as a key word. Studies were included in our review if they addressed either one or a combination of the three agents as the main focus in the context of hypertension therapy and if they in some way addressed the outcomes of interest noted above. Relevant data from these studies are reported descriptively. Other relevant references were acquired from bibliographic searches.

Results

The initial search in May, 2001 retrieved 844 citations from Medline. No additional studies were revealed in the Cochrane database. Of the Medline citations, 226 related to the use of prazosin, terazosin, or doxazosin in the context of antihypertensive therapy. The articles were grouped into descriptive categories created from useful summary topics or from recurrent themes noted in the trials that were pertinent to the outcomes of interest. These trial-based categories and the final count of the reported studies included: use in hypertension and prostatism-2 studies; weight and fluid status-14 studies; neurohormonal effects-5 studies; and epidemiological and clinical trial data-1 study.

Use in Hypertension and Prostatism

Evidence suggests that alpha-1 antagonists are frequently prescribed for hypertension, but there are few published data concerning the prevalence of the routine use of peripheral alpha-1 antagonists, the prevalence according to co-morbid conditions such as benign prostatic hypertrophy and the usual duration of therapy. In the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI), peripheral alpha-1 antagonists are recommended not only as second-line anti-hypertensive therapy after low-dose diuretics and beta blockers, but also for specific indications such as therapy in men with hypertension and prostatism [2]. Alpha-1 antagonists represent effective therapy for prostatism, and fifty percent of men have histologic evidence of BPH by 60 years of age [3,4]. The National Ambulatory Medical Care Survey reported that the number of people on any type of peripheral alpha-1 antagonist in 1995 was approximately 6 to 7% of those with hypertension [5]. About 80% of surveyed physicians would choose these drugs as a first-line blood pressure agent for patients with hypertension and symptoms of BPH [6].

Weight and Fluid Status

Peripheral alpha-1 antagonists were consistently associated with fluid retention. A 1984 study of prazosin reported by Bauer revealed increases in plasma volume, interstitial fluid volume, and extracellular fluid volume following both short-term and long-term therapy [7]. In this study of 14 hypertensive men, there was a significant 1.4 L average increase in ECFV, with a 200 mL average increase in plasma volume (measured with radioisotopic assays) that occurred within 3–6 weeks of initiation, lasted during 5 to 6 months of chronic therapy, and was still present during a two-week washout period. There was no weight change in that study, but two other studies demonstrated both an increase in weight as well as laboratory changes consistent with volume expansion for prazosin [8,9]. Bauer and his colleagues suggested that a net increase in total body sodium from an acute renal effect of prazosin was offset by a decrease in actual body weight. They also demonstrated that the fractional excretion of sodium was unchanged during treatment, and further suggested that the acute changes were followed by chronic sodium homeostasis and maintenance of the increased total body sodium.

The VA Cooperative Study on Antihypertensive agents was a double-blind, randomized controlled trial comparing atenolol, captopril, clonidine, diltiazem, hydrochlorothiazide, prazosin, and placebo for differences in antihypertensive efficacy in 1,105 men who had mild diastolic hypertension [10]. A highly significant weight gain of 1 kilogram was observed at 8 weeks with prazosin compared to baseline ($p < .001$), and this gain was also statistically significant when compared to the 8-week weight changes in all other groups that had experienced either weight loss or no mean weight change ($p < 0.05$). The prazosin arm had the highest rate of adverse effects, leading to discontinuation of treatment. The termination rate of 13.8% was higher than the termination rate from adverse effects for clonidine (10.1%), and significantly higher than the rates for captopril (4.8%), atenolol (2.2%), or hydrochlorothiazide (1.1%) [11]. The number of men treated with prazosin decreased from 62 at the beginning of the trial to 28 by the end. The average weight gain of 0.5 kilograms from baseline was no longer statistically significant at one year of therapy when compared to the original baseline weight or the other therapies.

Table 1: Weight Change with Terazosin

Study Type	N in study	Weight Change in Kg/ Number on therapy						Significance
		Total		Men		Women		
		n	Δ	n	Δ	n	Δ	
RCT								
Deger [8]	174	100		49	+1.4	51	+1.2	$p < .001$ from baseline
Sperzel [27]	865	569		438	+0.9	131	+0.4	$p < .05$ against placebo
Observational[*]								
Luther [28][†]	364	--	0 to +1.4					No statistical comparison
Mersey [29]	226	--	0 to +1.4					No statistical comparison
Withdrawal from therapy[‡]								
Ruoff [12]	27	13	-1.3					'statistically significant' from baseline in both
Ruoff [12]	69	32		19	-1.6	13	-1.6	

[*]Observational studies were open label, multicenter, follow-up studies of hypertensive patients on terazosin. [†]Trial demonstrated significant hemodilution by laboratory exams. [‡]Two different RCTs are reported, in which responders to terazosin were randomized to withdrawal of therapy and monitored.

Safety and tolerability trials with terazosin have shown similar results (Table 1). Patients treated with terazosin tended to gain about 1 kilogram from baseline on active therapy during these trials, and those on placebo therapy lost weight. Two of the randomized trials included a phase for withdrawal from active therapy, with weight information reported by Ruoff [12]. Withdrawal from active therapy was associated with a loss of 1.3 kilograms.

Doxazosin has also been associated with volume expansion. A physiology study reported by Lund-Johansen demonstrated a plasma volume fluid expansion of about 10% when compared to baseline values [13]. Larger randomized controlled trials have also consistently demonstrated that patients treated with doxazosin gain weight, as summarized in Table 2. While patients treated with doxazosin tend to gain weight, patients on placebo therapy lost weight. The Treatment of Mild Hypertension Study (TOMHS) trial is a notable exception for the trend towards weight gain [14]. All five treatment groups and the placebo group received intensive dietary counseling aimed at weight loss, and all groups lost weight without significant differences between trial arms.

Neurohormonal and Cellular Effects

Physiologic studies with small numbers of participants are by nature underpowered to detect meaningful population differences, but may provide a starting point when such data are not available. Peripheral alpha-1 antagonists were associated with perturbations in neurohormonal levels in various studies. In particular, peripheral alpha-1 antagonists are associated with an increase in plasma norepinephrine in diverse patient populations, as summarized in Table 3. This table reflects increases in norepinephrine in normotensive patients, hypertensive patients, and patients with chronic congestive heart failure from a variety of these small studies.

Several lines of evidence suggest that elevated catecholamine levels are cardiotoxic [15]. Elevated plasma norepinephrine levels are hypothesized to cause direct myocardial damage through many mechanisms, which may be amplified by concomitant alpha-1 blockade. In rats, norepinephrine stimulates apoptosis, which is mediated through beta receptors [16]. In addition, alpha-1 cardiac receptors inhibit this response in rat myocytes [17]. The increased concentration of norepinephrine leading to cardiac beta receptor stimulation combined with alpha-1 receptor inhibition may lead to increased apoptosis in myocytes.

Other hormones that are associated with cardiovascular disease are affected by peripheral alpha-1 antagonists. Endothelin-1 is a vascular hormone, which may play a role in the generation and maintenance of heart failure [18]. In hypertensive patients, doxazosin lowers von Willebrand factor commensurate with blood pressure, but it does not

Table 2: Weight Change with Doxazosin

Study	Number of subjects	Type of Study	Weight change in kilograms (number on therapy)			
			Doxazosin	Placebo	Other therapy	p-value¶
Ames [30]	147	RCT	+1.5 (n = 73)	-0.2 kg (n = 74)		'significant'
ABC trial [31]*	191	RCT	+ 1.16 (n = 96)		-0.04, atenolol (n = 95)	p = .019
Ott [32]	126	RCT	+2.0 (n = 63)		+ 0.9, atenolol (n = 63)	NS
Torvik [33]	172	RCT	+ 0.04 ± 0.2 (n = 58)	-1.18 ± 0.29 (n = 57)	+0.21 ± 0.2, prazosin (n = 57)	p < .001 for treated groups
TOMHS [34]†	902	RCT	-3.1 (n = 134)		-3.9, chlorthalidone (n = 136)	NS

Comparison made by intention to treat; patients on doxazosin withdrawing from the ABC study (n = 39) had a mean weight gain of 2.21 kg. †Trial included diet therapy for weight loss. ¶p for comparison between groups and not from baseline.

Table 3: Increase in Norepinephrine (NE) with Peripheral Alpha-1 Antagonists

Study population	Reference	Study design	Drug	N	Findings
Normotensive	Takata [35]	observational	doxazosin	8	Trend towards increase in NE with therapy; 60% decrease in NE after withdrawal of therapy
Hypertensive	Izzo [36]	comparative	prazosin	8	50% increase in NE; 0.9 kg wt gain
			captopril	8	12% decrease in NE, 0.82 kg wt loss, p < 0.01 for comparison
CHF	Colucci [37]	observational	prazosin	10	Increase in NE from 145 ± 133* to 481 ± 376 with therapy
	Stein [38]	observational	prazosin	8	Increase in NE from 276 ± 347 to 521 ± 130 with therapy
	Markham [39]	RCT	prazosin	25	Treatment group NE increased from 790 ± 280 to 1413 ± 1030 after four weeks of therapy; placebo group was 749 ± 315 at baseline and 772 ± 596 at four weeks, p for difference at four weeks = 0.08.

* Values for NE are given in pg/mL.

lower high levels of endothelin-1 while atenolol does [19].

Other mechanisms for cellular injury have been suggested. Hooper proposed that peripheral alpha-1 antagonists alter cellular repair mechanisms, possibly causing cardiac damage. He noted that prazosin blocks heat shock protein expression in myocardium, and it has been hypothesized that this may leave myocardium more vulnerable to injury [20].

Epidemiological and Clinical Trial Data

Between 1966 and 2001, there were 188 published cardiovascular randomized controlled trials related to the treatment of hypertension with the use of peripheral alpha-1 antagonists. Among these, only ALLHAT specifically assessed differences in cardiovascular endpoints resulting from control of hypertension with a peripheral alpha-1 antagonist. Most of these trials focused on surrogate endpoints such as equivalence of blood-pressure reduction and effects on cholesterol. Other studies focused on tolerability and pharmacology. There are no case control, cohort, or other studies that analyzed the impact of these

agents on cardiovascular endpoints. Using data from other trials may offer a partial framework for the interpretation of newer findings.

ALLHAT demonstrated a highly statistically significant, near doubling in the incidence of heart failure in the doxazosin arm compared to heart failure occurrences in the chlorthalidone arm. Although there was no difference in the primary outcome of CHD or the secondary outcome of total mortality, there were small but statistically significant increases in the secondary outcomes of angina (RR 1.16, 95% CI 1.05–1.27) and stroke (RR 1.19, 95% CI 1.01–1.40). Since ALLHAT is a comparative trial, we know that doxazosin is associated with more adverse cardiovascular outcomes than low-dose chlorthalidone, but we do not know how doxazosin might compare with placebo. The SHEP trial, however, does provide a comparison between chlorthalidone and placebo therapy for a reference point of heart failure, although the study populations have different demographic and blood pressure distributions [21]. The SHEP trial included 4,736 people aged 60 and older who had a systolic blood pressure of 160 to 219 mmHg and a diastolic blood pressure of less than 90 mmHg. Subjects were randomized to low-dose diuretics or placebo, and were followed for an average of 4.5 years for major CV events. Comparisons between those randomized to active therapy and those on placebo demonstrated nearly a 50% reduction in fatal and nonfatal heart failure events (RR 0.51, 95% CI 0.37–0.71). The rates of CHF in SHEP participants treated with diuretics and placebo were 5 and 10 per 1,000 person-years, respectively. In comparison, the rates of CHF in ALLHAT participants treated with diuretics and doxazosin were 10 and 20 per 1,000 person-years, respectively. If low-dose chlorthalidone has a similar risk reduction in the ALLHAT population, and halves the incidence of clinical heart failure events compared to no therapy, the effect of doxazosin would be comparable to that of the placebo arm in the SHEP trial.

Conclusions

The report of the doxazosin arm termination in ALLHAT was published in April, 2000. At that time, the results of the ALLHAT trial were unexpected, given the potential association between high dose diuretics and the risk of sudden death [22], and the favorable effect of peripheral alpha-1 antagonists on lipid profiles [14]. Comparing data from other studies suggests the possibility that the beneficial effects of peripheral alpha-1 antagonists for lowering blood pressure may be nullified by a negative effect, or that other antihypertensives have positive actions beyond their antihypertensive effects. Those treated with doxazosin in ALLHAT had a mean blood pressure that was 2 to 3 mmHg higher than the mean blood pressure of those treated with chlorthalidone. Based on Framingham Heart Study logistic regression coefficients, this 2 to 3 mmHg difference in systolic blood pressure is associated with an increased relative risk of only 1.06 to 1.09 [23]. From available data, it appears that this average difference in systolic blood pressure is not large enough to double the average incidence of CHF.

The literature suggests several mechanisms by which peripheral alpha-1 antagonists in general and doxazosin in particular might prove inferior to other types of antihypertensive therapy. They are associated with a mild volume expansion, which may precipitate the clinical presentation of heart failure in those with subclinical disease. If this is the mechanism responsible for increasing the incidence of CHF in the ALLHAT trial, it would be consistent with the early divergence of the Kaplan-Meier curves in that study.

Peripheral alpha-1 antagonists also cause neurohormonal changes during chronic therapy. The long-term ramifications of these changes for patients being treated for hypertension are not known. These drugs appear to cause increases in norepinephrine, and this increase may nullify the beneficial effect of lowered blood pressure on the occurrence of CHF. Not only are increased plasma catecholamines a central feature in heart failure, they are now a recommended target for effective life-prolonging therapy [24–26].

Given that doxazosin is not as effective as chlorthalidone in reducing the cardiovascular complications of hypertension, several questions remain. There is still a paucity of information regarding the absolute risk reduction for clinical heart failure or other cardiovascular events afforded by peripheral alpha-1 antagonists in a variety of populations. Differentiation of the mechanism for reduced protection compared to diuretics would be interesting but difficult to accomplish. For heart failure in particular, the increase in symptomatic episodes of CHF may be due to hemodynamic effects of doxazosin unmasking incipient heart failure, direct myocardial injury, or both. Chronic volume loading may not only unmask subclinical ventricular dysfunction, but may possibly contribute to worsening ventricular function over time.

Whatever mechanisms were responsible for the heart failure findings in ALLHAT, the results support the current national recommendations to use low-dose diuretics or beta-blockers as first line agents for the pharmacologic treatment of uncomplicated hypertension.

Competing Interests

Dr. Psaty was a Merck/SER Clinical Epidemiology Fellow (co-sponsored by the Merck Co. Foundation, Rahway, NJ, and the Society for Epidemiologic Research, Baltimore,

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